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REARRANGEMENT REACTION OF 2-METHYLTETRAHYDRO-PYRANS HAVING A C1'-MESYLOXY GROUP ON THE C2-SIDE CHAIN WITH ZINC ACETATE: RING EXPANSION AND RING OPENING REACTIONS

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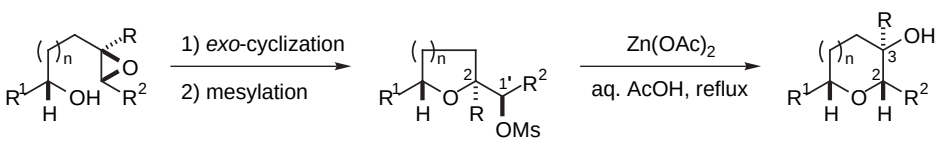
Abstract — Rearrangements of four possible stereoisomers of 6-*tert*-butyl-2-(1'-mesyloxy)ethyl-2-methyltetrahydropyran with $Zn(OAc)_2$ in aq. AcOH were investigated. Rearrangement-ring expansion and/or rearrangement-ring opening reactions took place depending on the stereostructure of the substrates.

The cyclic ether system is an important component among a large number of organic compounds. Particularly, marine polycyclic ethers represented by brevetoxins[1] have recently attracted the attention of synthetic organic chemists due to their unusual structural framework, novel functionalities, and potent biological activities. The most characteristic feature of this class of marine natural products involves *trans*-fused polycyclic ether ring systems. Thus, various methods for constructing these systems have been extensively studied. We have developed an efficient method for the synthesis of 2,3-*trans*-tetrahydropyrans (**3a**; n=1) and oxepanes (**3a**; n=2) based on a $Zn(OAc)_2$-mediated rearrangement-ring expansion of 1',2-*anti*-tetrahydrofurans (**2a**; n=1) and tetrahydropyrans (**2a**; n=2) having a C1'-mesyloxy group, respectively, which were prepared by *exo*-cyclization of epoxy alcohols (**1a**) (Scheme 1).[2]



1a: R = Me
1b: R = H
n = 1, 2

2a: R = Me
2b: R = H

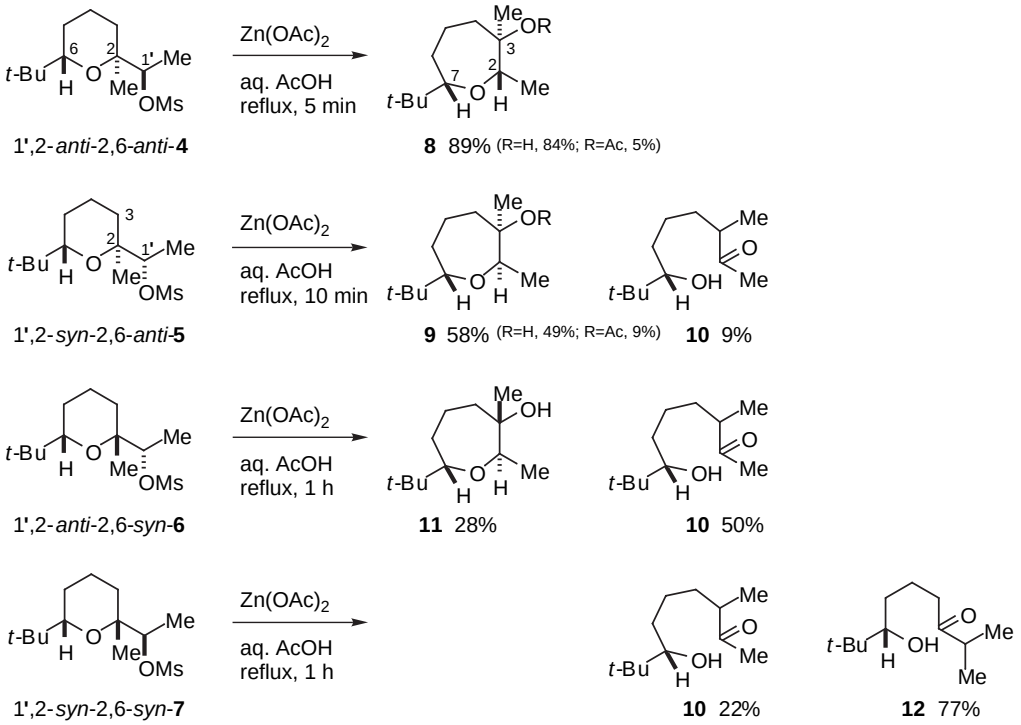
3a: R = Me
3b: R = H

Scheme 1

We recently revealed that, in the case of various stereoisomers of tetrahydropyrans (**2b**; n=2) having no C2-methyl group, rearrangement-ring expansion and/or rearrangement-ring opening reactions took place depending on the stereostructure of the substrates.[3] Thus, only the 1',2-*anti*-2,6-*anti*-tetrahydropyran (**2b**; n=2) afforded the ring-expanded oxepane (**3b**; n=2) and most substrates gave a ring-opened ketone as a main product by migration of C2-hydride to the C1'-position. We now report on $Zn(OAc)_2$-mediated reactions of the four possible stereoisomers of tetrahydropyrans (**2a**; n=2) having a C2-methyl group.

In order to investigate the present rearrangement in more detail, we chose the four possible stereoisomers of 6-*tert*-butyl-2-(1'-mesyloxy)ethyl-2-methyltetrahydropyrans (**4**-**7**),[4] which have a *tert*-butyl group at the C6-position as an equatorial anchor to fix the conformation of the ether ring. Thus, the four stereoisomers (**4**-**7**) have an axial or equatorial C2-side chain with *anti*- or *syn*-configuration of C2-methyl and C1'-mesyloxy groups.

First, the reactions of the 2-methyltetrahydropyrans (**4** and **5**) having an axial C2-side chain were examined (Scheme 2). Treatment of the 1',2-*anti*-2,6-*anti*-tetrahydropyran (**4**) with $Zn(OAc)_2$ in AcOH-H_2O (1:1) at reflux effected rearrangement with ring expansion within only 5 min to give the 2,3-*trans*-2,7-*syn*-oxepane (**8**) in 89% combined yield (R=H, 84%; R=Ac, 5%). The corresponding 1',2-*syn*-tetrahydropyran (**5**) was also treated under the same reaction conditions (10 min) to give the 2,3-*cis*-2,7-*anti*-oxepane (**9**) in 58% yield along with a methyl ketone (**10**) in 9% yield. Then, the 2-methyltetrahydropyrans (**6** and **7**) having an equatorial C2-side chain were examined. The reactions of



Scheme 2

6 and **7** required rather longer time (1 h) for completion than those of **4** and **5** having an axial side chain. The 1',2-*anti*-2,6-*syn*-tetrahydropyran (**6**) gave the ring-expanded 2,3-*trans*-2,7-*anti*-oxepane (**11**) in 28% yield and the ring-opened methyl ketone (**10**) in 50% yield. On the other hand, 1',2-*syn*-isomer (**7**) gave no ring-expanded ether but gave ring-opened products, the methyl ketone (**10**) and an isopropyl ketone (**12**), in 22 and 77% yields, respectively.

These results revealed that the rearrangement-ring expansions stereospecifically take place in **4**, **5**, and **6** to give the stereoisomers of oxepanes (**8**, **9**, and **11**), respectively.[5] These stereospecific ring expansions would proceed through 1) formation of bicyclooxonium ions (**i**, **ii**, and **iii** in Figure 1) by stereoselective participation of ether oxygen to the C1'-position leaving the C1'-mesyloxy group and 2) regio- and stereo-selective attack of H_2O or AcOH at the C2-position of the resultant bicyclooxonium ions, respectively. Production of the methyl ketone (**10**) and isopropyl ketone (**12**) from **5**, **6**, and **7** resulted from 1) leaving of the C1'-mesyloxy group, 2) rearrangement of the C2-C3 bond and the C2-methyl group to the C1'-position, respectively, and 3) successive addition of H_2O at the C2-position.

Conformational analyses of the stereoisomers (**4**-**7**) were attained by detailed NMR measurements.[6] These observations suggested the conformers (**4a**, **5b**, **6a**, **6b**, and **7c**) would certainly exist. The selected NOE data are shown in Figure 1. Based on these conformational analyses, the results of the present rearrangement were considered.

The NOE observation between the C1'- and C6-protons in **4** revealed that **4** mainly takes a conformation (**4a**) having antiperiplanar relationship between the C2-O and C1'-OMs bonds. The bicyclooxonium ion

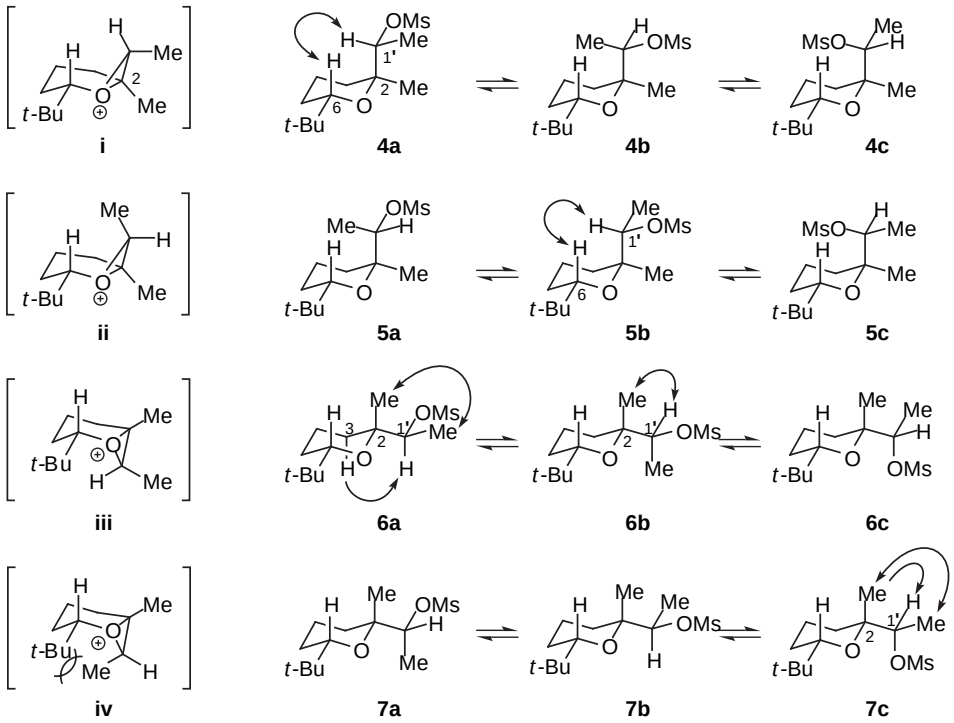


Figure 1

(**i**) could be easily formed by participation of ether oxygen from the conformation (**4a**). Then, regio- and stereoselective addition of H_2O or AcOH to the tertiary C2-position took place to give the ring-expanded ether (**8**). Although a conformation (**5b**) was mainly observed in **5**, the ring-expanded ether (**9**) was obtained as the main product *via* a bicyclooxonium ion (**ii**), which could be formed as soon as a conformation (**5a**) was set by bond rotation at the reaction temperature.[7] Since the oxirane is orientated to pseudoaxial position of the tetrahydropyran in the bicyclooxonium ion, the substrates having an equatorial side chain require a flipping at the C2-position to form the bicyclooxonium ion. Therefore, formation of the bicyclooxonium ion from the substrates having an equatorial side chain is presumed to be more difficult than those having an axial side chain. Indeed, the ring-expanded ether (**11**) was a minor product although a conformation (**6a**) was observed in **6**. Particularly, formation of a bicyclooxonium ion (**iv**) should be very difficult in the case of **7**, because of its steric hindrance. Thus, the ring-expanded ether was not produced from **7**. The ring-opened ketones (**10** and **12**) were obtained from other conformations (**5b**, **6b**, **7b**, and **7c**) by migration of the C2-C3 bond and the C2-methyl bond antiperiplanar to the mesyloxy group to the C1'-position, respectively.

In summary, treatment of the four possible stereoisomers of 6-*tert*-butyl-2-(1'-mesyloxy)ethyl-2-methyltetrahydropyrans with $Zn(OAc)_2$ in aq. AcOH led to rearrangement-ring expansion and/or rearrangement-ring opening reactions depending on the stereostructure of the substrates. The ring expansion of the 1',2-*anti*-2,6-*anti*-tetrahydropyran (**4**) having an axial C2-side chain took place most effectively to give the 2,3-*trans*-2,7-*syn*-oxepane (**8**). When the substrates incur difficulty in the formation of the bicyclooxonium ion, the C2-C3 or C2-methyl bond migrates to the C1'-position. This knowledge should be helpful in designing a synthetic route to natural products having cyclic ethers using the current rearrangements.

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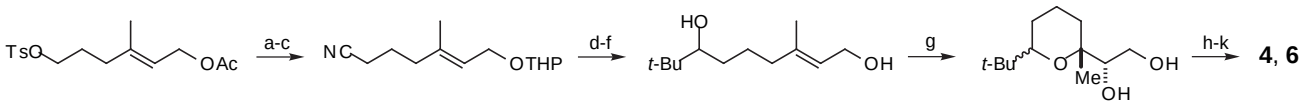
4. The 1',2-*anti*-mesylates (**4** and **6**) were synthesized as racemic compounds *via* the known tosylate starting from geraniol (K. Mori and Y. Nakazono, *Liebigs Ann. Chem.*, 1988, 167). The 1',2-*syn*-mesylates (**5** and **7**) were synthesized starting from nerol by the same procedure.



Reagents and conditions: a) NaCN, DMSO, 80 °C (100%); b) K_2CO_3, MeOH, rt (95%); c) DHP, CSA, CH_2Cl_2, 0 °C (73%); d) DIBAH, CH_2Cl_2, -78 °C to 0 °C (81%); e) *t*-BuMgCl/THF, toluene, 0 °C (95%); f) CSA, MeOH, rt (100%); g) *m*CPBA, CH_2Cl_2, rt, then CSA (90%); h) TsCl, Py, $CHCl_3$, 0 °C; i) $LiAlH_4$, Et_2O, rt; j) separation of diastereomers (46 and 47% yields of each isomer in 2 steps); k) MsCl, Et_3N, CH_2Cl_2, 0 °C (83% for **4**, 70% for **6**).

5. The structures of **8**, **9**, and **11** were confirmed by their NMR analyses (NOE, HMQC, and HMBC). Data for **8** (R=H): ^{1}H NMR (600 MHz, C_6D_6) δ 3.19 (q, *J*=6.4 Hz, 1H), 2.87 (dd, *J*=10.0, 4.1 Hz, 1H), 1.59 (br dd, *J*=12.7, 9.3 Hz, 1H), 1.35-1.57 (m, 5H), 1.14 (d, *J*=6.4 Hz, 3H), 1.04 (s, 3H), 0.90 (s, 9H); ^{13}C NMR (150 MHz, C_6D_6) δ 90.1, 83.7, 75.1, 43.7, 35.1, 30.8, 26.3, 23.1, 20.7, 15.8. Data for **9** (R=H): ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.68 (q, *J*=6.4 Hz, 1H), 3.34 (dd, *J*=11.7, 4.9 Hz, 1H), 1.82 (ddd, *J*=13.7, 7.8, 4.9 Hz, 1H), 1.76 (ddd, *J*=13.7, 4.4, 2.0 Hz, 1H), 1.70 (dddd, *J*=14.2, 7.8, 4.4, 2.9 Hz, 1H), 1.54 (dddd, *J*=14.2, 13.2, 11.7, 2.0 Hz, 1H), 1.49 (ddd, *J*=13.7, 11.7, 11.7 Hz, 1H), 1.32 (ddd, *J*=13.7, 13.2, 2.9 Hz, 1H), 1.14 (d, *J*=6.4 Hz, 3H), 1.05 (s, 3H), 0.92 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 86.5, 73.0, 72.7, 44.5, 36.3, 27.3, 26.8, 25.7, 21.5, 16.1. Data for **11**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.72 (q, *J*=6.8 Hz, 1H), 3.31 (dd, *J*=9.8, 5.4 Hz, 1H), 1.35-1.80 (m, 6H), 1.20 (d, *J*=6.8 Hz, 3H), 1.14 (s, 3H), 0.90 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 83.1, 76.1, 75.1, 43.1, 36.2, 28.2, 26.6, 22.1, 21.5, 15.0.
6. The NOE, $^3J_{HC}$, and $^3J_{CC}$ were measured at room temperature. PFG-HMBC (or long-range PFG-HMQC without decoupling) and PFG-INADEQUATE were applied to the compounds (**4**-**7**) at natural abundance to observe the $^3J_{HC}$ and $^3J_{CC}$, respectively.
7. This result suggested that the participation of ether oxygen would be faster than migration of the C-C bond.